Single trial SI and SII responses evoked by median nerve stimulation

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1 Introduction

We have previously demonstrated that the single trial responses to identical simple auditory stimuli are heterogeneous forming distinct sets of responses with very robust distribution for each subject, but very different across subjects [1]. The main auditory response takes place at latencies approaching 100 ms, so the variability in this case can be explained by complex interactions between regions well after the first arrival of the stimulus induced activity at the cortex in the first 20 milliseconds. We report here our study of single trial responses in the somatosensory system. In this system the role of distinct cortical areas, specifically the first (SI) and second (SII) somatosensory cortices are better delineated [2,3]. The activation in SI can be robustly identified early (within 20-30 ms) while the SII activation is best identified 70 to 100 ms later, with some discussion about its presence at earlier latencies. We focus on the single trial activations in SI and SII and track changes in the left and right hemisphere during the first 200 ms after the onset of a weak and strong electrical stimulus is applied to the left and right median nerve in separate runs.

2 Methods

Three healthy right-handed male subjects (S1-3, ages 48, 52, 55) volunteered for the MEG experiment. Two different strengths of electrical pulses (duration 0.2 ms, inter stimulus interval 1.0 s) were applied in turn to the left and right median nerves at the wrist. The stimulation levels were determined by the subject's sensation (just felt; F) and movement (small twitches; T) levels. The weak level was defined as F+0.25×(T−F), while the strong level was T+0.25×(T−F). Total of four recording runs was made, one for each arm and level. One and three hundred trials were delivered respectively at the strong and weak level.

The CTF whole head system (151 channels) was used to record MEG signals from the subjects 300 ms before the onset of the stimuli for 800 ms, sampled at 1250 Hz with an online filter of 0-200 Hz. EEG electrodes were also used to monitor subject's artifacts from eye blinks (EOG), heart beats (ECG) and movements (EMG). The environmental noise (e.g. power line) was first removed and then the data were band-pass filtered 1-200 Hz (1-50 Hz for S2) using the CTF software. Average signal was constructed for each run on the trigger onset (-200 to 400 ms). A set of 30 single trials was also extracted, which was made up of the first 10, middle 10 and last 10 trials of the run. Independent component analysis (ICA) [4] was used to remove subject artifacts from the single trial data. Magnetic field tomography (MFT) [5] was applied to both the average and single trial signals (-200 to 400 ms at a step of 0.8 ms, and 1.6 ms for S2). For each subject, three hemispherical source spaces were defined, each covering the left, right and top part of the brain well. The spatially overlapping estimates from the three source spaces were combined into one covering the entire brain.

3 Results

Figure 1 shows the MFT solutions extracted form the average signal and the t-maps obtained from pixel by pixel analysis of the 30 single trial MFT solutions around the early SI activation (N20) latency. In general the average and single trial MFT solutions show a large spread of activity which mainly contains areas around BA 3b and 40. The t-maps are more focal showing tight foci in distinct areas, e.g. the sensory and motor area S1 in figure 1. We have defined the ROI center from the average signal and used a radius of 1 cm which therefore encompasses more than one of the tight foci seen in the statistical maps. Table 1 lists four ROIs we defined for the three subjects. Activation curves for the modulus of the current density and along the main direction in the ROIs were calculated as a function of time.

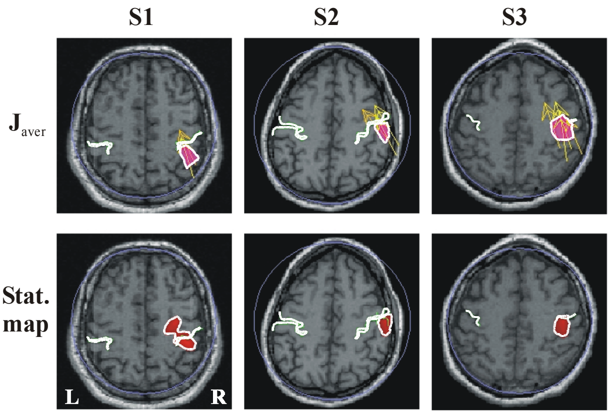

Figure 1: *Early SI activations for left arm strong stimulation on MRI with central sulcus outlined. The top row shows instantaneous MFT solutions extracted from the average signal. The bottom row shows the statistical significance maps from t-test (white outline corresponds to* $p < 0.000000001$*).*

Table 1: *Talairach coordinates (mm) of ROI centers.*

Subj. ROI	S1	S2	S3
L SI	-41 -33 58	-57 -37 42	-43 -32 54
R SI	42 -33 49	55 -17 41	48 -30 49
L SII	-42 -7 24	-58 -29 16	-56 -6 27
R SII	53 -7 8	56 -11 16	64 -20 21

Table 2: *Classification of SI and SII responses. Within each cell the change in mean activity (normalized to the standard deviation) is shown and labeled as even (=) if the responses at the beginning, middle and end of the run are within 70% of the maximum response, habituated (h) if the response decreases monotonically as the run progresses, facilitated (f) if the response increases monotonically as the run progresses and modulated (m) if the response is differently modulated. Mean activity less than one standard deviation throughout the first 200 ms after stimulus onset is considered too noisy for classification and is marked by *.*

Stim. ROI	subj.	L arm strong	L arm weak	R arm strong	R arm weak
L SI	S1	*	*	2.5 =	3.2 h
	S2	1.0 h	*	2.7 =	1.4 h
	S3	1.0 =	*	1.8 h	1.2 h
L SII	S1	*	*	1.2 =	1.0 =
	S2	2.0 h	1.3 =	3.2 h	1.7 h
	S3	*	1.0 h	1.7 h	1.2 h
R SI	S1	2.7 f	1.1 =	*	*
	S2	3.5 m	1.1 m	2.0 h	1.2 m
	S3	2.0 m	1.2 =	1.0 m	1.2 h
R SII	S1	*	*	*	*
	S2	1.4 h	1.3 h	1.7 h	*
	S3	2.4 h	1.7 h	1.0 =	*

For each ROI the significance of the activation in each set of single trials was evaluated by computing at each timeslice the inverse of the instantaneous coefficient of variation, i.e. the ratio of the mean versus standard deviation. If this ratio was above unity for at least 5-10 ms in the interval 10 to 200 ms., then responses were classified further according to how they changed as the run progressed.Figure 2 shows early and late single trial activations in contralateral SI and SII for right arm strong stimulation for subject S2. The details of the variability differed from subject to subject but when only activity with normalised instantaneous mean above 1.5 was considered a broadly consistent picture emerged, as summarised in Table 2. The clearest pattern emerges from contralateral stimulation for both SI and SII.

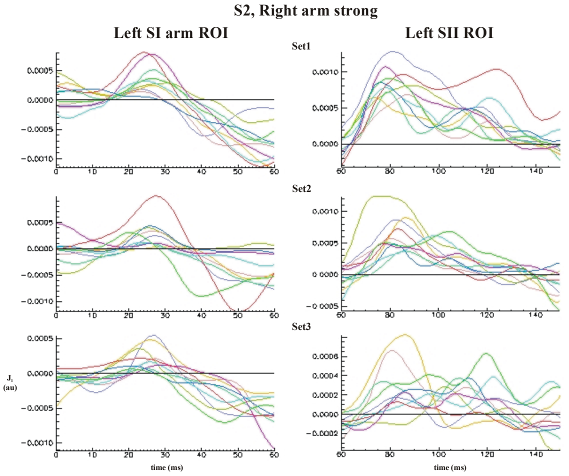

Figure 2: *Activation curves for the three sets of single trial data from subject S2. The activations are separated into groups from trials 1-10 (top), 45-55 (middle) and 88-98 (bottom). A running average was used to eliminate sharp variations.*

Figures 3 shows in more detail the full variation in the responses for left hemisphere S1 for strong and weak contralateral stimulation. For strong stimulation there is habituation early on for one subject (S2) but only a weak one for the other two subjects at latencies after 100 ms. In contrast a strong habituation is present for all subjects in the first 100 ms for weak stimulation. Figure 4 shows the corresponding results for contralateral stimulation (strong and weak) in the left hemisphere SII activation. A strong habituation is only seen in two subjects (S2 and S3) for contralateral stimulation (strong and weak).

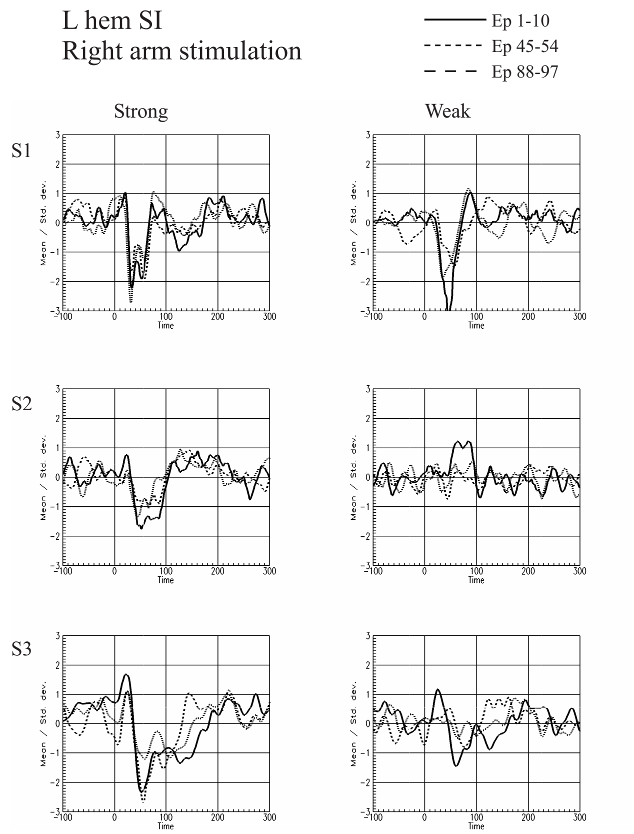

Figure 3: *Mean response across groups of trials for contralateral SI from stimulation of the right arm for all subjects. Strong and weak stimulation results are on the left and right respectively.*

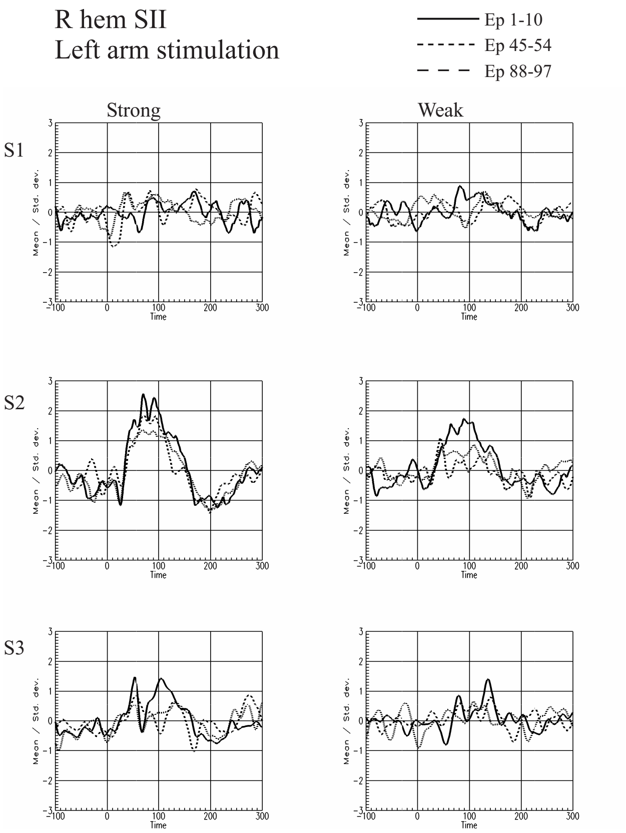

Figure 4: *Mean response across groups of trials for contralateral SII from stimulation of the left arm for all subjects. Strong and weak stimulation results are on the left and right respectively.*

4 Discussion

We have studied the activation of sensory cortex following weak and strong stimulation of the arm. The study located single trial somatosensory evoked magnetic fields (SEF) in the same brain areas as most recent fMRI and averaging MEG studies [2,3]. MFT solutions extracted from the average and single trial instantaneous signal were more extended than the foci of statistically significant activity obtained from the pixel by pixel analysis of MFT solutions across single trials. In the temporal domain single trial responses were of shorter duration compared to the averaged ones, but the details of the short term changes were highly variable. A broadly consistent picture emerges when attention is focused on sets of single trial responses with stable (over 5-10 ms) mean activity well above one standard deviation. Strong decrement of responses is seen in SII in both hemispheres, while for SI a decrement is only seen on the left hemisphere and especially for weak stimulation. While the SII decrement is described before [6], to our knowledge the SI dependence on hemisphere and strength of stimulation was not previously identified, possibly because only strong stimuli were used.

The SEF were not found to vary across 5 states distinguished by the degree of ongoing mu oscillatory activity [7] while atention and related processes are known to affect SII responses more than SI, as seen in studies of fMRI [8], monkey electrophysiology [9] as well as human MEG [10] and intracranial recordings [11]. The response decrement may therefore be attributed to decreasing vigilance of our subjects in the course of the experiment Alternatively it may constitute a specific process of long term habituation by sensory circuits detecting the absence of novelty in the repeated stimuli. The later case is suggested by the fact that the decrement in our study was area specific in single trials.

It is difficult to evaluate the significance of the reported SEF slow decrement with time before establishing its underlying mechansm(s). The averaged SEF varies with the stimulus repetition rate [12]. If the degree of single response attenuation varies also with the repetition rate, then the attenuation may contribute to the process of temporal discrimination. In this respect SII was reported to function more efficiently than SI [13]. Beyond its possible contribution to learning processes, in which SII may have a prominent role [14], a long term habituation might contribute to (and its measurement might help quantify) the "sensory gating", a process which is considered to be defective in schizophrenia [15]

In conclusion, single trial analysis of SEF offers opportunities for studying the interaction of the many areas in normal sensory processing and sensory learning, which are far greater than those allowed by the analysis of averaged responses. Our results are also relevant to the parallel versus serial SI and SII activation debate, in as much as they point out that a single time-independent view of the sequencing of events in the brain – as presently allowed by averaging - is misleading.

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